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INVESTIGATING HOW SPECIFIC CLASSES OF RETINAL CELLS CONTRIBUTE TO VISION WITH A MULTI-LAYERED SIMULATOR

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Thanks to the astonishing functional and anatomical diversity within retinal neuronal classes, our brain can recreate images from interpreting parallel streams of information emitted by the retina. However, how these neuronal classes interact to perform these functions remains largely a mystery.

To track down the signature of a specific cell class, we employ a novel experimental approach that is based on the ability to pharmacologically control the level of neural activity in specific subgroups of retinal ganglion cells (RGCs), specialized cells which connect the retina to the brain via the optic nerve and amacrine cells (ACs), interneurons that modulate RGCs activity over a wide area via lateral connectivity. We modified the activity of Scnn1a- and Grik4-expressing RGCs and ACs through excitatory DREADD (Designer Receptors Exclusively Activated by Designer Drugs) activation using clozapine-n-oxide (CNO). We hypothesize that modifying the activity of RGCs and/or ACs may not only affect the individual response of these cells, but also their concerted activity to different stimuli, impacting the information sent to the brain, thereby shedding light on their role in population encoding of complex visual scenes. However, it is difficult to distinguish the pharmacological effect on purely experimental grounds when both cell types express DREADDs and respond to CNO, as these cells "antagonize" each other. Contrarily, modeling and numerical simulation can afford it.

To this end, we have developed a novel simulation platform that can reflect normal and impaired retinal function (from single-cell to large-scale population). It is able to handle different visual processing circuits and allows us to visualize responses to visual scenes (movies). In addition, it simulates retinal responses in normal and pharmacologically induced conditions; namely, in the presence of DREADD-expressing cells sensitive to CNO-induced activity modulation.

Firstly, we deploy a circuit that models different RGCs classes and their interactions via ACs and emulates both their individual and concerted responses to simple and complex stimuli. Next, we study the direct (single-cell) or indirect (network) pharmacological effect when the activity of RGCs and/or ACs is modified in order to disentangle their role in experimental observations. To fit and constrain the numerical models and check their validity and predictions, we use empirical data. Ultimately, we expect this synergistic effort (1) to contribute new knowledge on the role specific subclasses of RGCs play in conveying meaningful signals to the brain, leading to visual perception and (2) propose new experimental paradigms to understand how the activation of ensembles of neurons in the retina can encode visual information.

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